Proteomics for NAM-to-Human Translation of Drug Disposition and Toxicity



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Conflict of Interest Disclosure

- Bhagwat Prasad is cofounder and CSO of Precision Quantomics, Inc.

All models are wrong, but some are useful.

- **The industry challenge**
  - ❑In vitro models often **lack biological authenticity**
  - ❑In silico models often **scale uncertainty instead of truth**

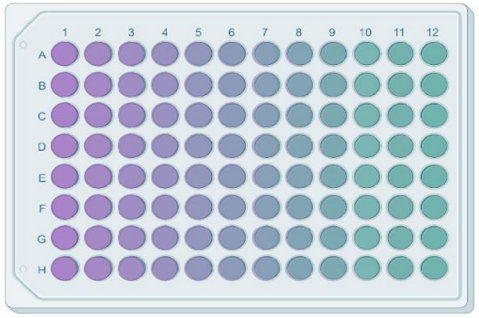
- **Reproducibility crisis is often driven by:**
  - ❑Poor model characterization
  - ❑Hidden biological drift

    - ***If the biology is wrong, the model will fail.***

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Why NAMs: Opportunities and Challenges

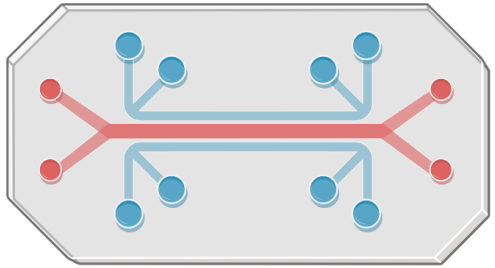
- NAMs are central to modern drug development and regulatory science
- NAMs generate rich mechanistic, molecular, and functional data
- Increasing regulatory acceptance requires **quantitative translation**, not qualitative interpretation



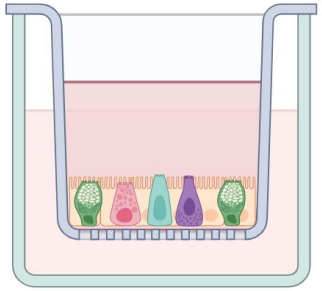
In vitro models



Organoids



Microphysiological Systems (MPS)



3D Cultures

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Proteomics for NAM-to-Human Translation

	NAM Systems	Human Tissues
Data types available	Activity assays and **protein abundance**	Primarily **protein abundance**
Feasibility of activity assays	High and experimentally flexible	Limited and technically challenging

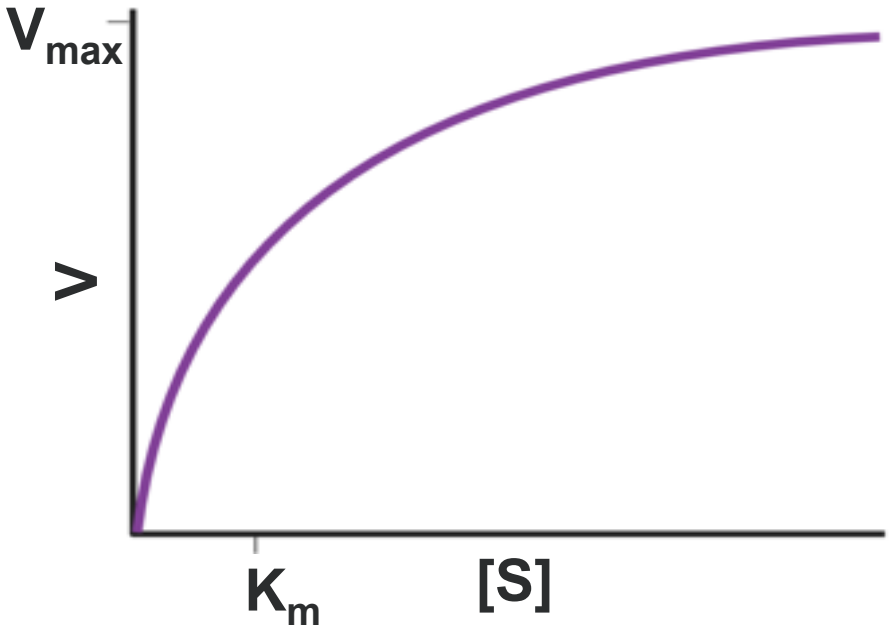
$$CL_{int} \alpha [E]$$

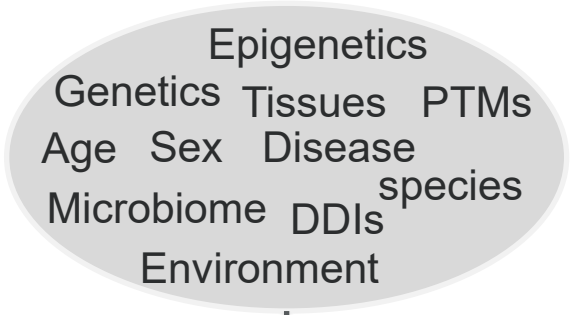
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Enzyme/Transporter Abundance and Drug Clearance

$CL_{int} \propto V_{max} \propto [E]$





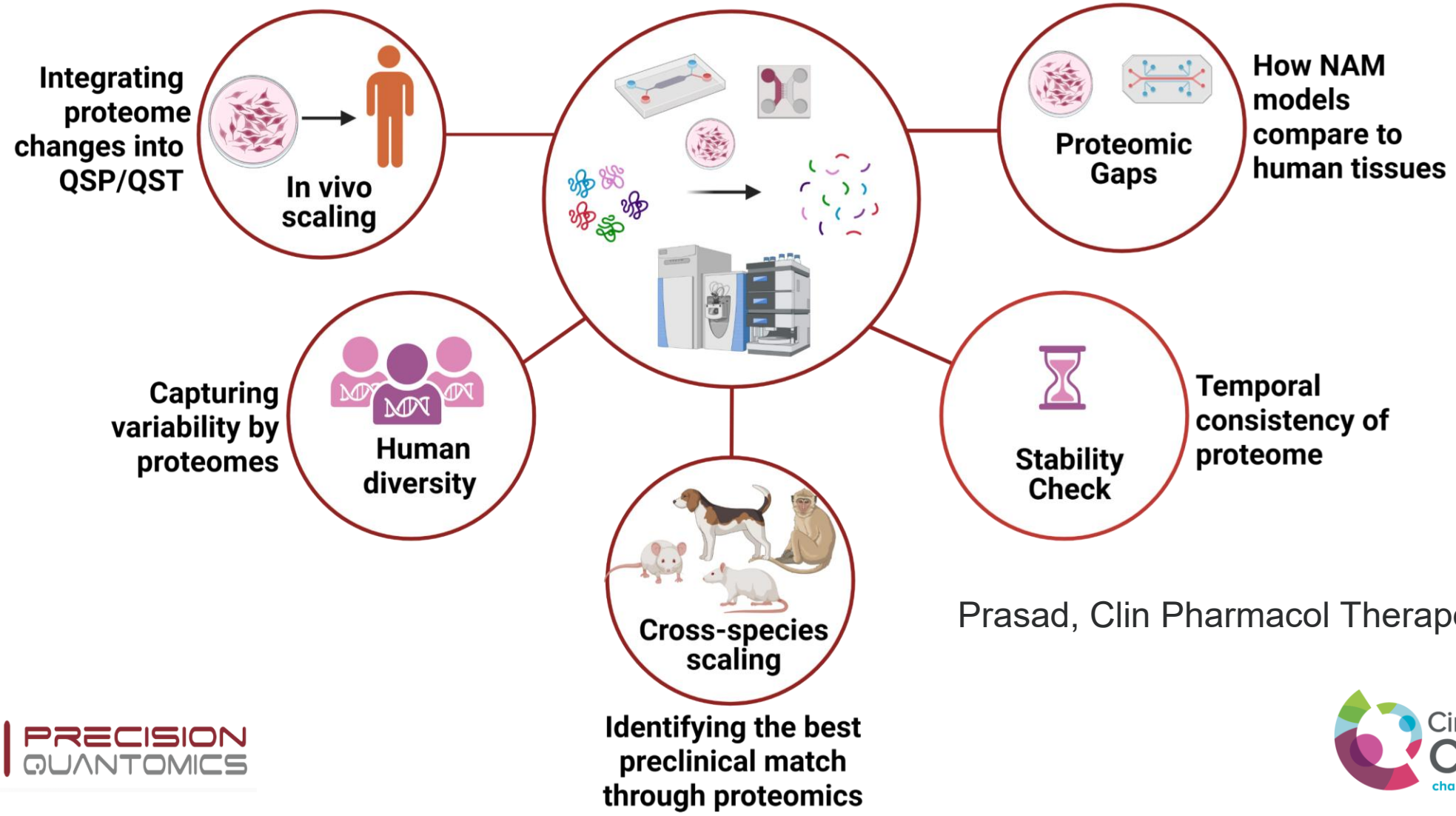
Enzyme Abundance [E]

$$CL_{int} = \frac{V_{max}}{K_m + [S]}$$

SNP/PTMs, inhibition/activation, species



Promise of Quantitative Proteomics in Characterizing In Vitro NAMs

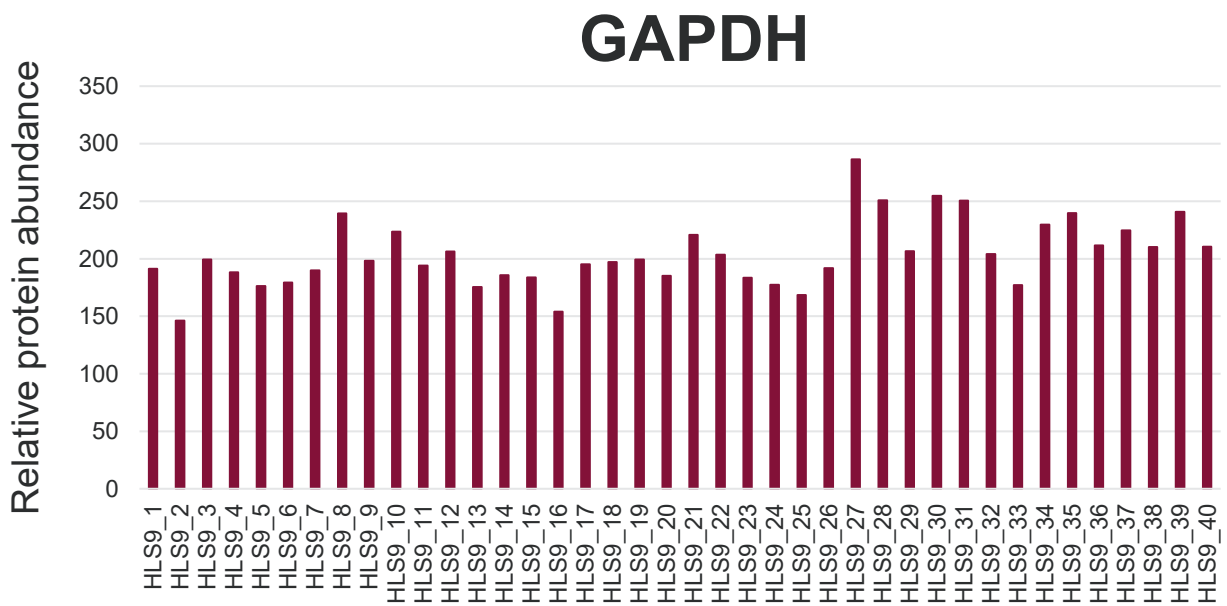


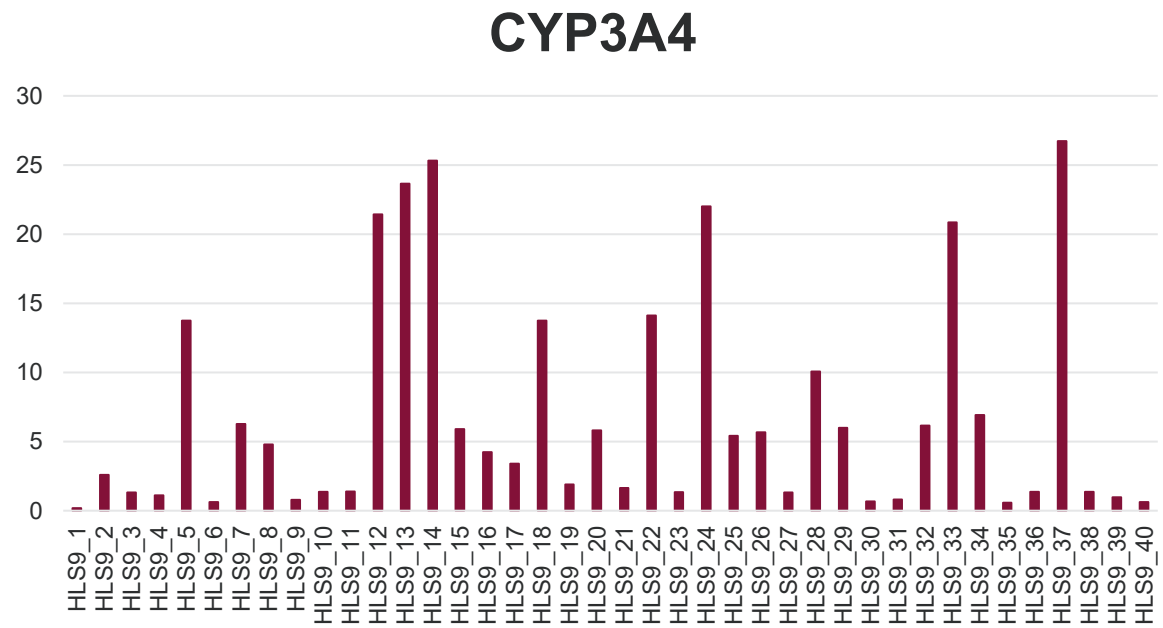
Prasad, Clin Pharmacol Therapeut, **2025**

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Interindividual Variability in Liver Enzyme Abundance





Representative 40 biobanked human liver samples

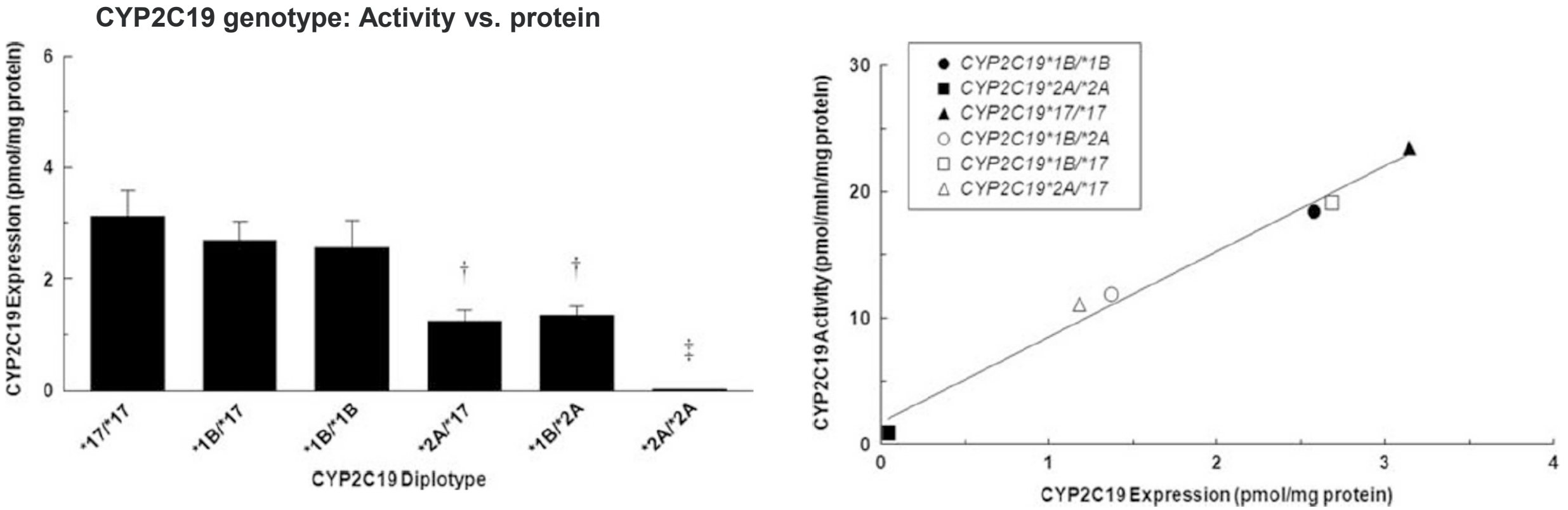
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$$CL_{int} \propto [E]$$

Darshak Gadara

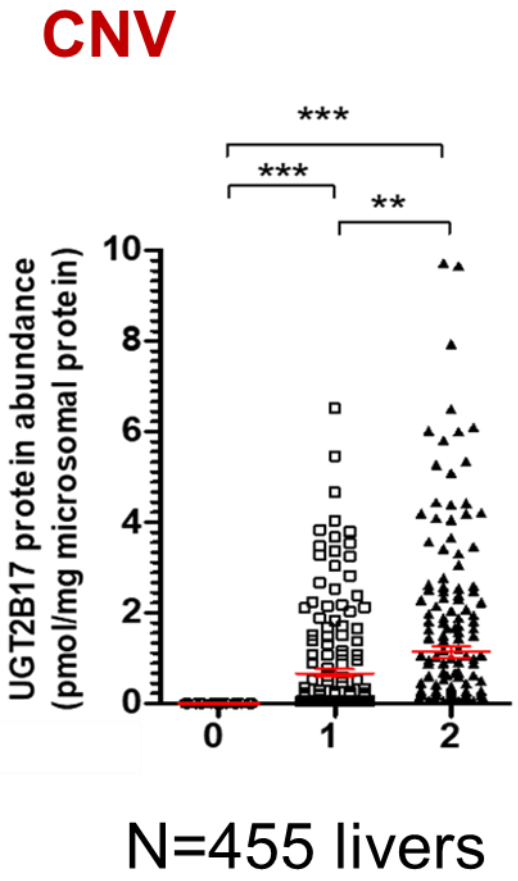
Griffin Shaffer

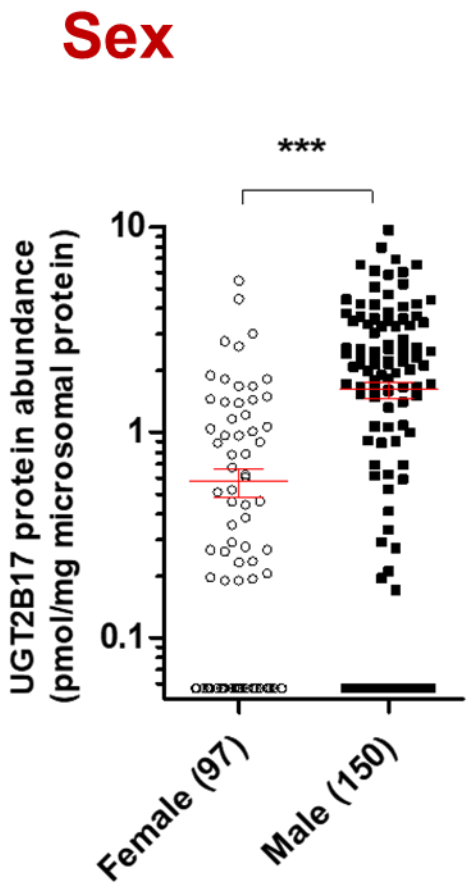
Does protein abundance correlate with functional activity?

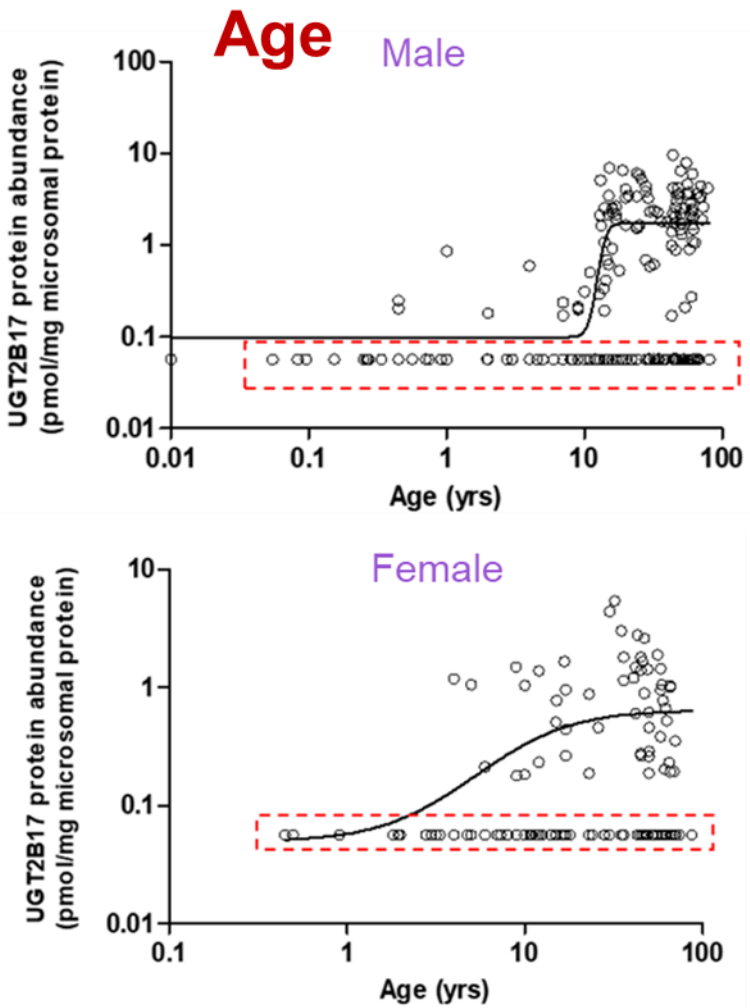


Shirasaka et al., Pharmacogenomics J, **2016**.

Interindividual Variability (e.g., UGT2B17)





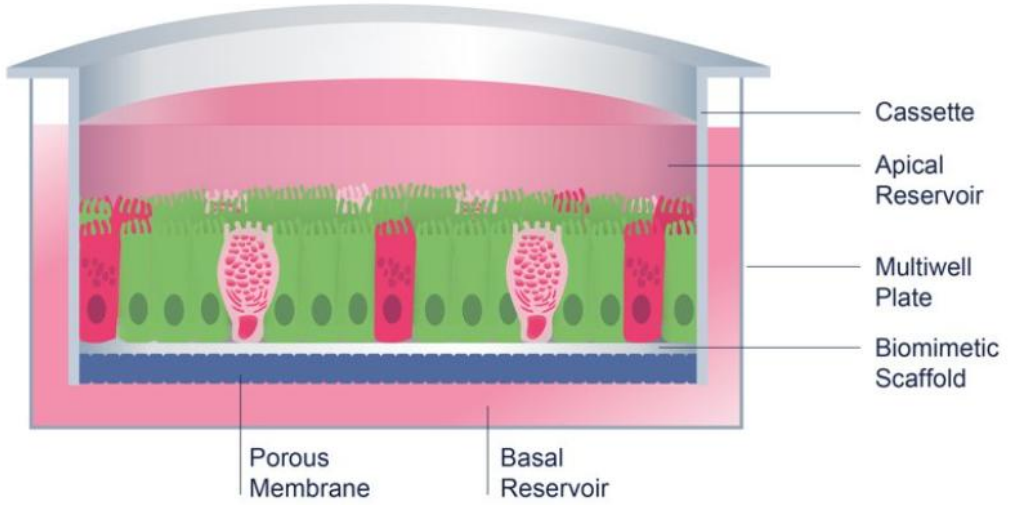


Protein abundance data correlate with mRNA expression and activity

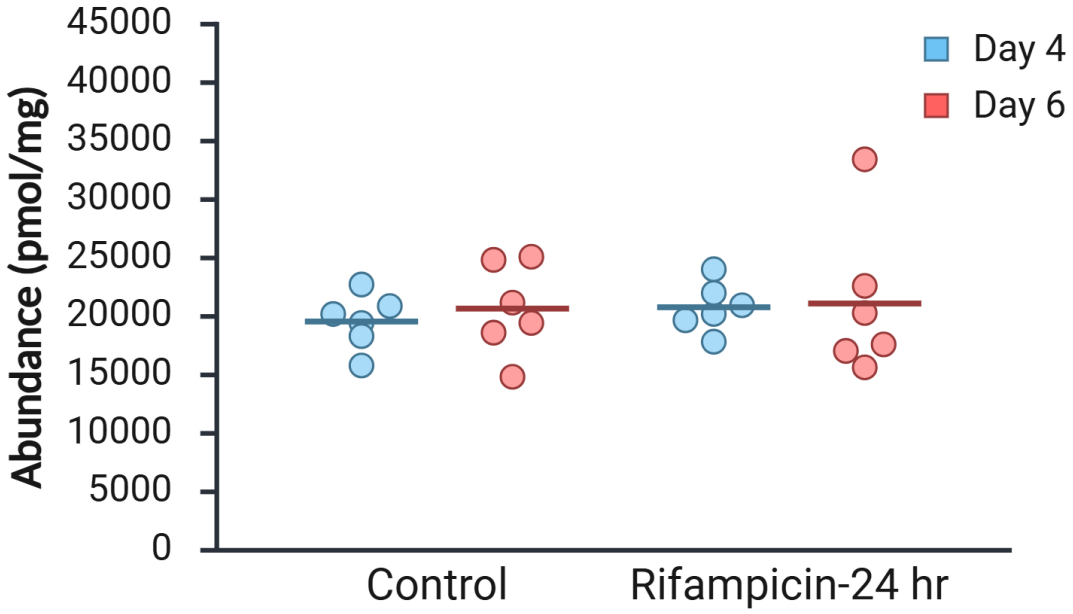
Bhatt et al., Drug Metab Dispos, **2018.**

Context of use: CYP Induction

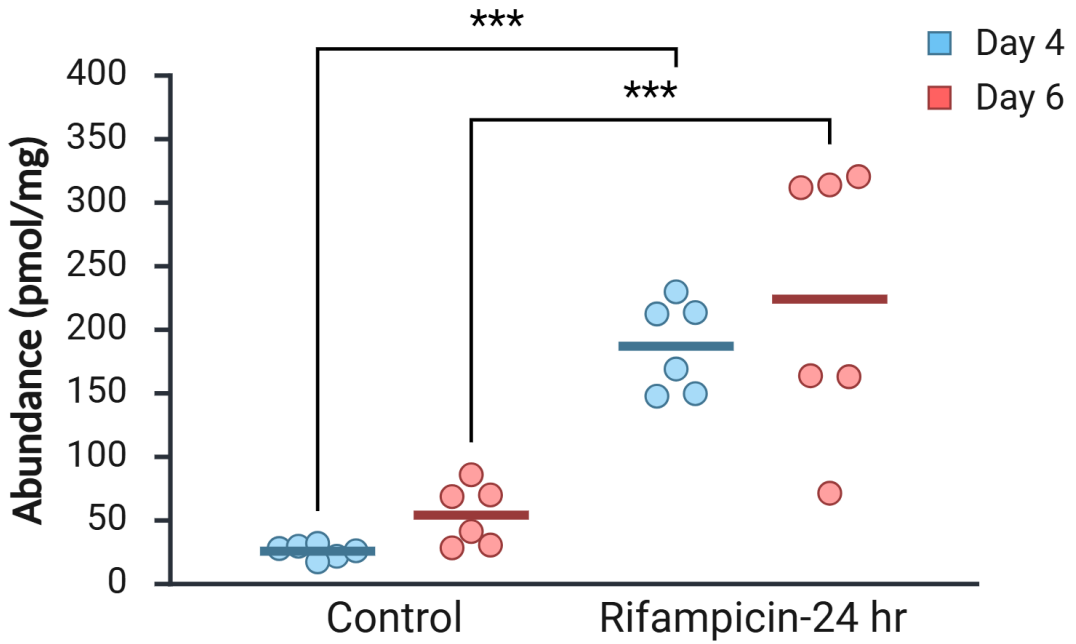
ALTIS Biosystem's RepliGut
Human Intestinal Epithelial Cell Model



GAPDH

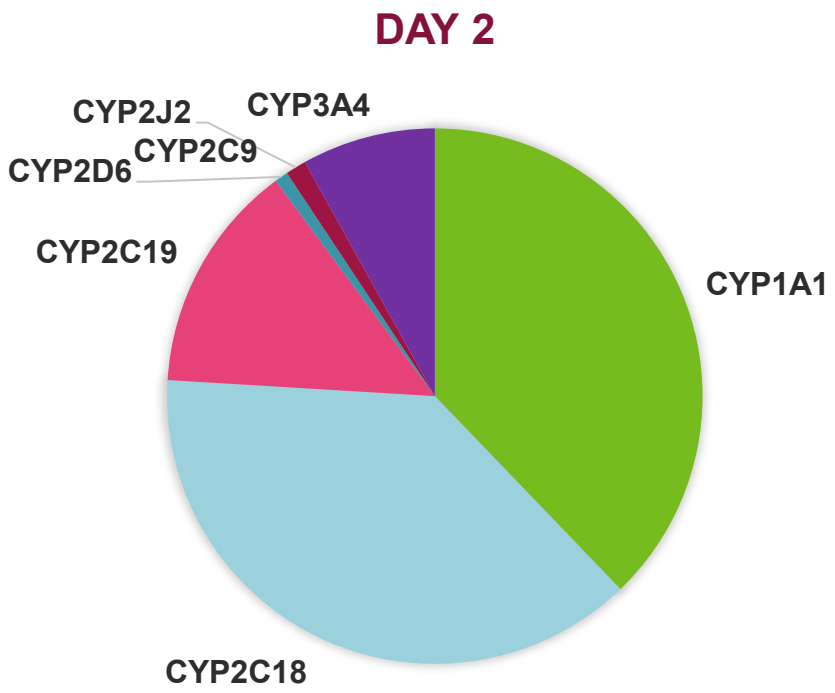


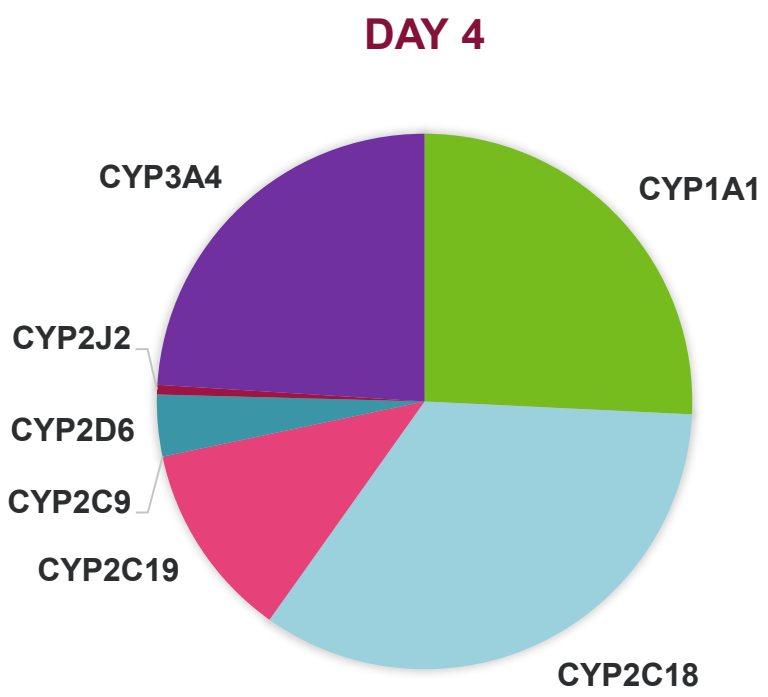
CYP3A4

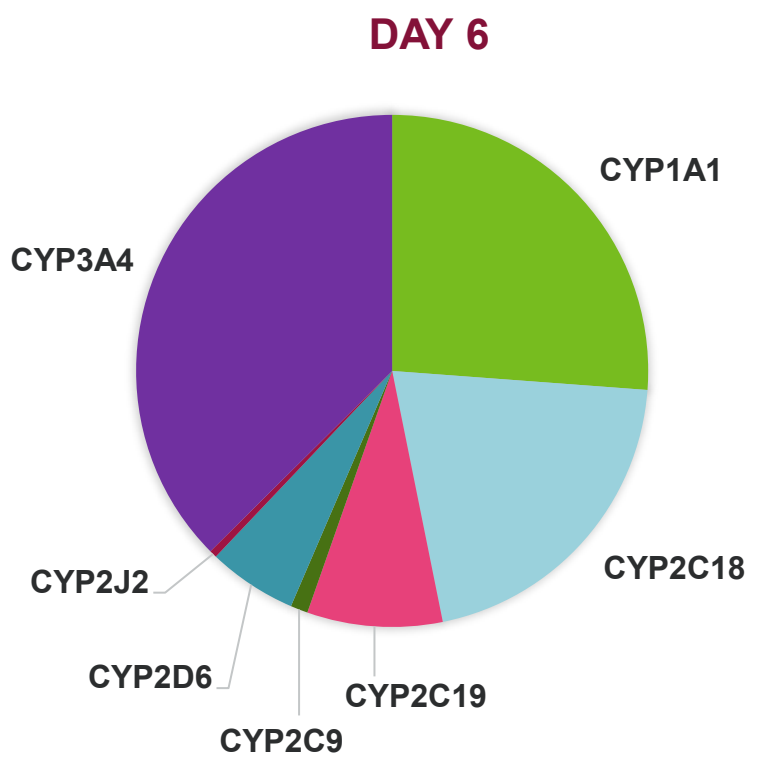


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Effect of Culture Duration on CYP450 Composition in a Human Intestinal NAM Model

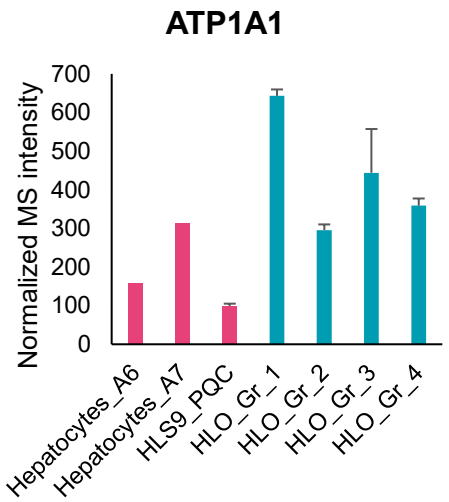


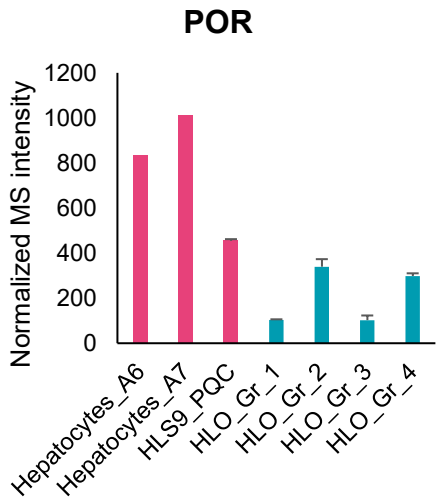


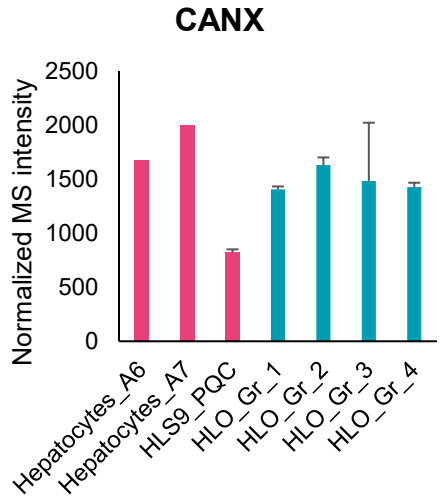


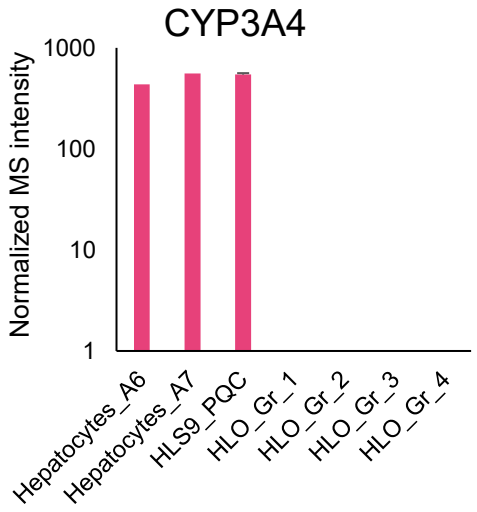
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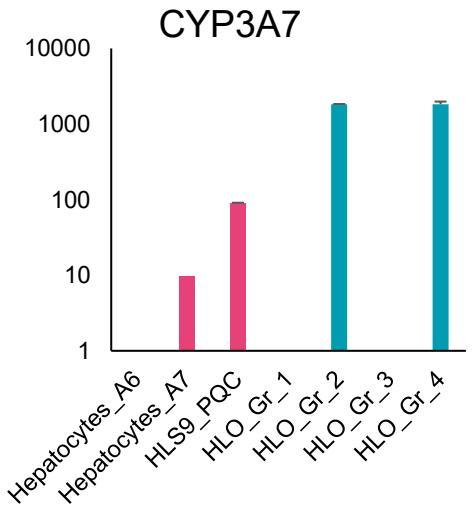
Do iPSC-derived liver organoids (HLOs) represent adult human liver?

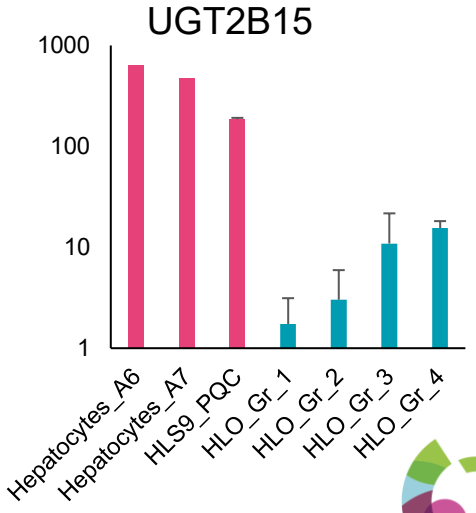












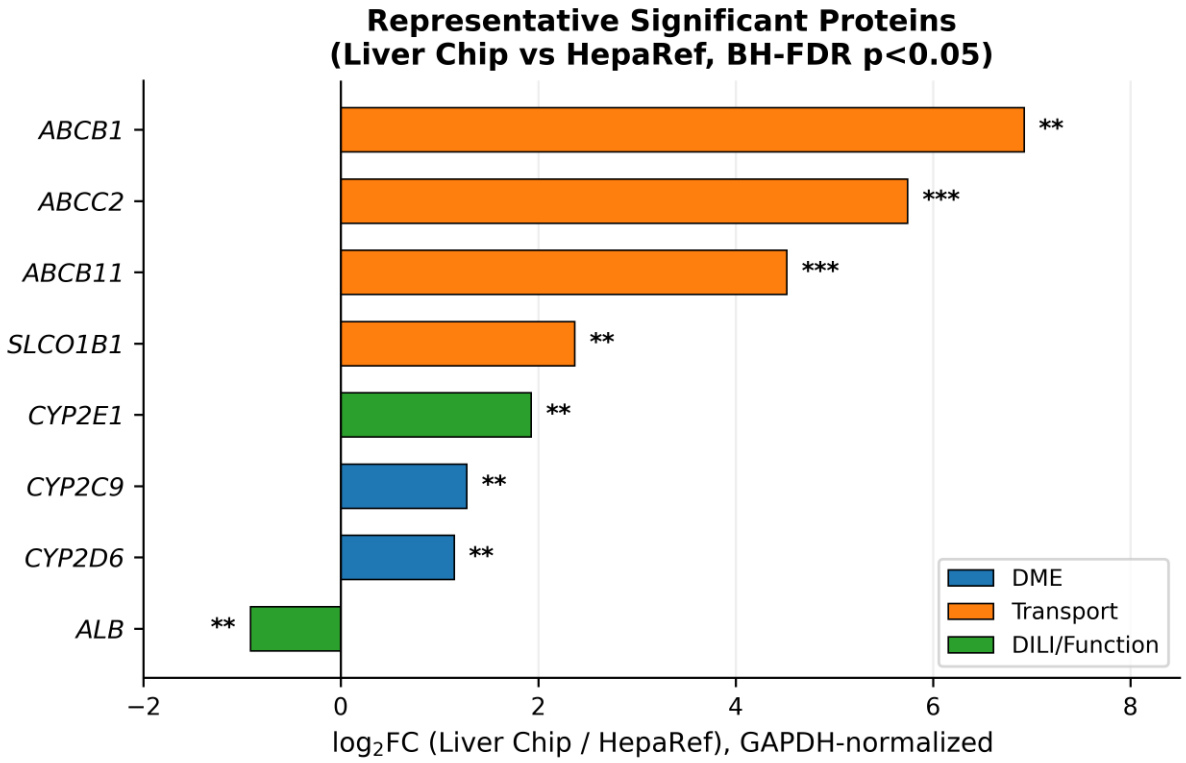
Group 1 and Group 3 (Conventional method)
Group 2 and Group 4 (Optimized method)

Collaborators: Takanori Takebe and Masaki Kimura

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DMET abundance in hepatocyte NAMs (Liver-Chip and MASLD models)

Liver Chip



Control vs. MASLD model

Protein	Control	MASLD	HepaRef
CYP1A2	1.52	**3.23***	1.33
CYP2A6	1.36	2.27	1.84
CYP2B6	0.091	**0.232***	0.472
CYP2C19	0.038	0.027	0.180
CYP2C8	0.268	0.216	1.24
CYP2C9	1.25	1.77	3.94
CYP2D6	0.281	0.292	1.18
CYP2E1	11.01	7.39	4.69
CYP3A4	17.00	25.65	8.44
CYP3A5	8.11	11.82	3.73
CYP4A11	0.327	0.320	1.65

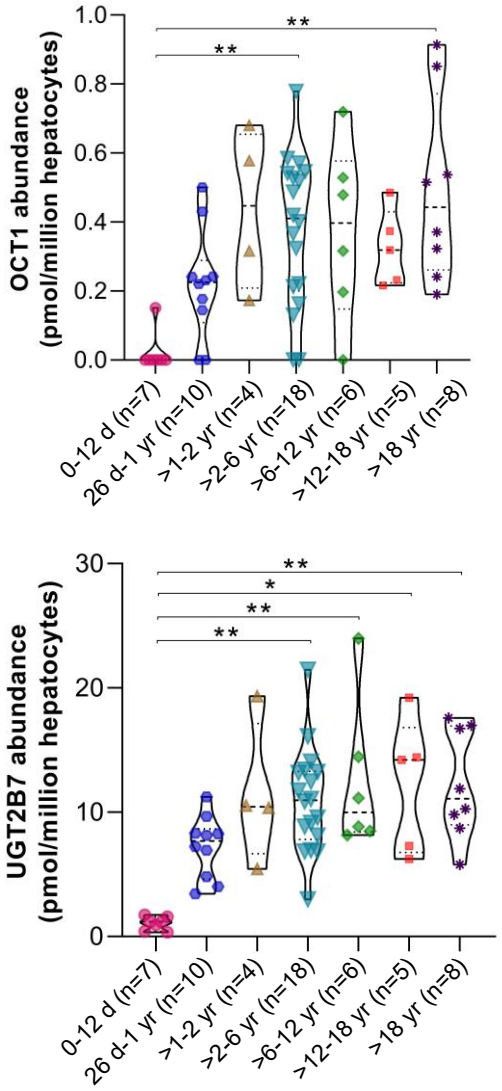
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HepaREF model : Precision Quantomics' reference standard

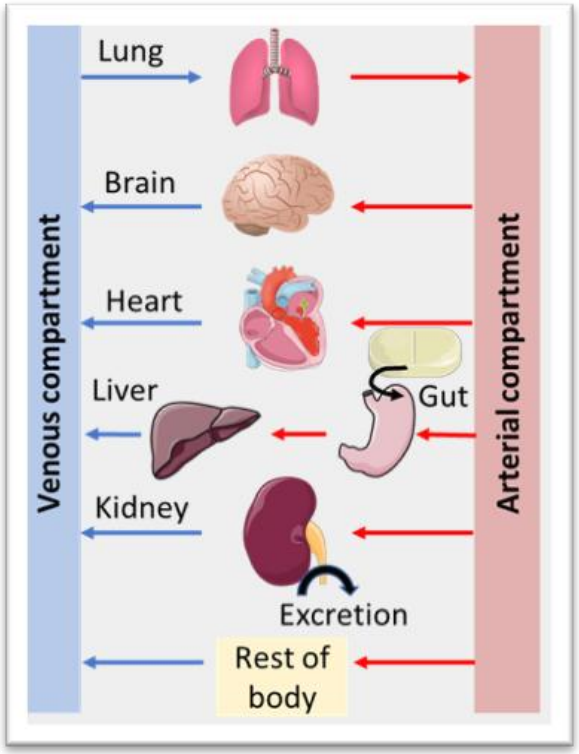
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Proteomics-informed PBPK Modeling

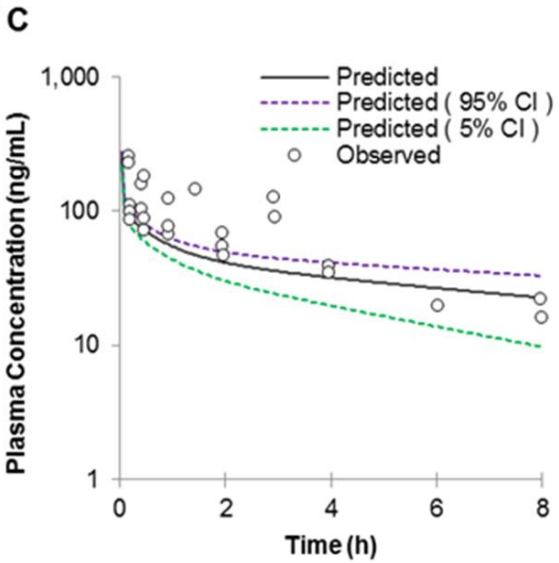
- PBPK models are:
  - Human-focused
  - Mechanistic
  - Tissue-resolved
- PBPK is the natural integration platform for NAM data
- Without PBPK integration, NAM outputs remain:
  - System-specific
  - Difficult to extrapolate to humans
  - Hard to use for dose prediction and risk assessment



Physiologically-based pharmacokinetic model



Morphine dose prediction in newborns



Thakur et al., Clin Pharmacol Ther. **2024.**
Bhatt et al., Clin Pharmacol Ther. **2018.**

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molecular pharmaceutics

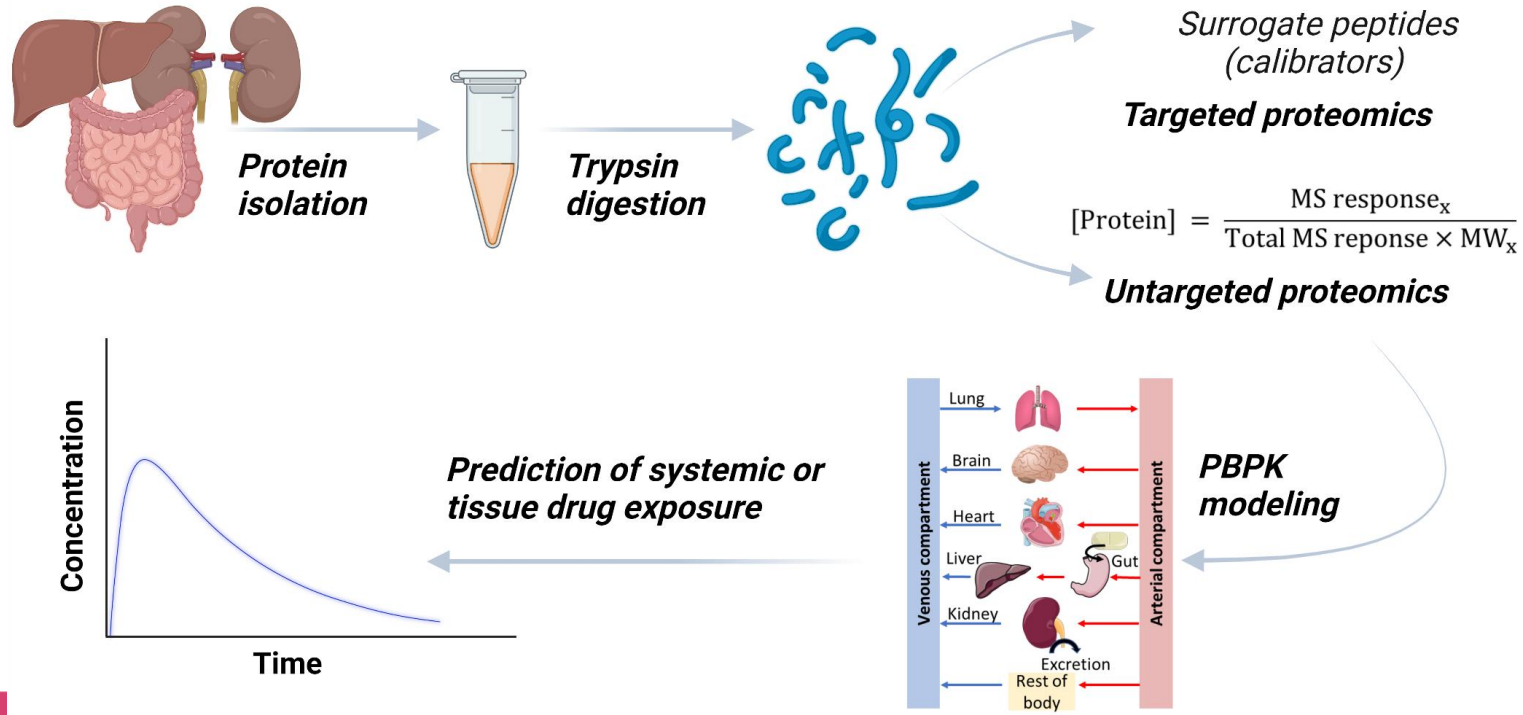
pubs.acs.org/molecularpharmaceutics

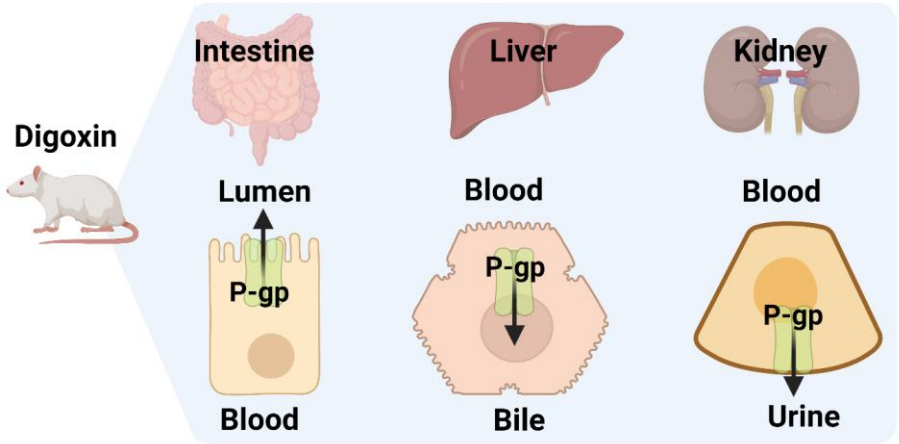
Article

Quantitative Characterization of Clinically Relevant Drug-Metabolizing Enzymes and Transporters in Rat Liver and Intestinal Segments for Applications in PBPK Modeling

Sheena Sharma, Dilip K. Singh, Vijay S. Mettu, Guihua Yue, Deepak Ahire, Abdul Basit, Scott Heyward, and Bhagwat Prasad*

PK-Sim®

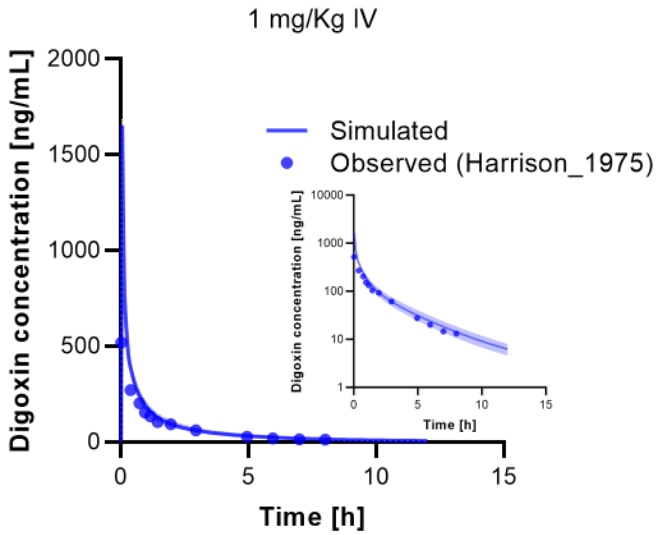


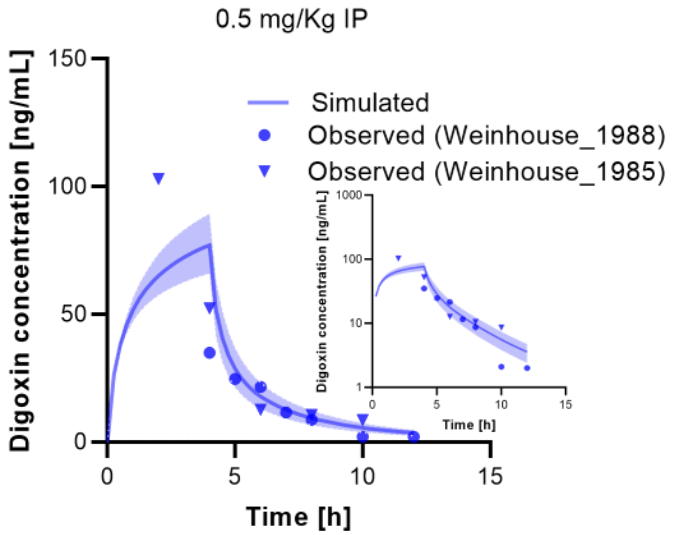


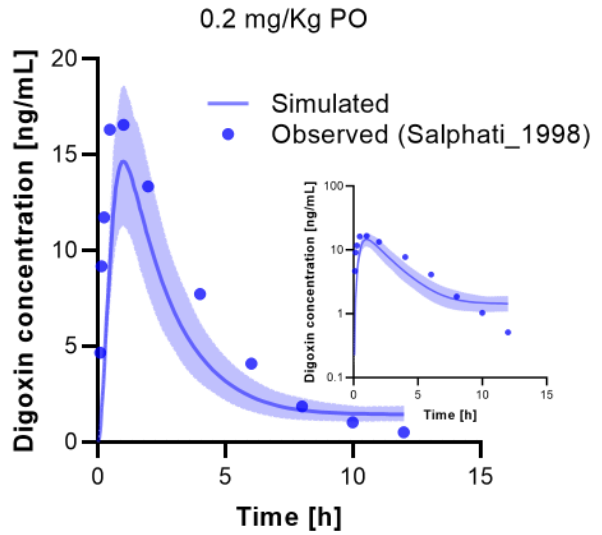
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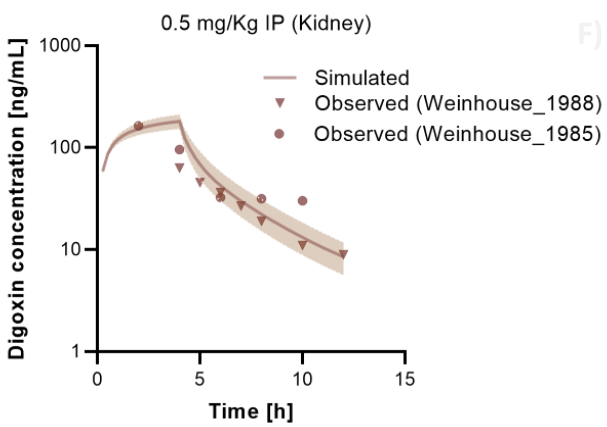
Quantitative Characterization of Clinically Relevant Drug-Metabolizing Enzymes and Transporters in Rat Liver and Intestinal Segments for Applications in PBPK Modeling

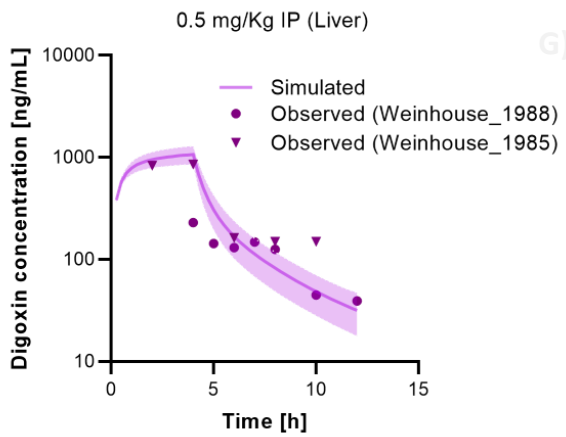
Sheena Sharma, Dilip K. Singh, Vijay S. Mettu, Guihua Yue, Deepak Ahire, Abdul Basit, Scott Heyward, and Bhagwat Prasad*

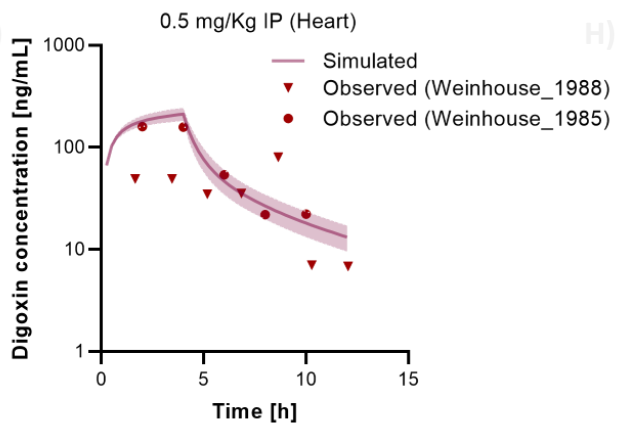


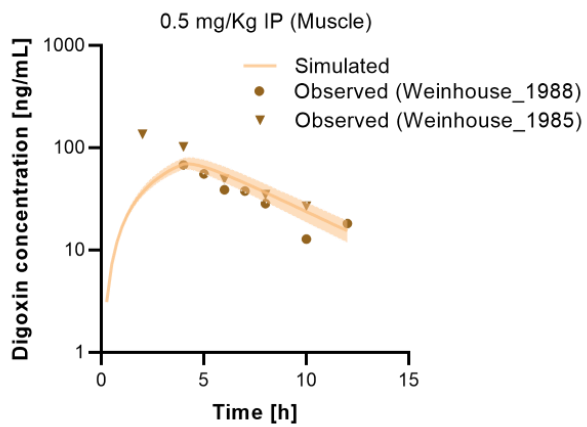












Proteomics-Informed NAM-to-Human Translation

Protein abundance as the bridge from In Vitro NAMs to PBPK / QSP-QST predictions

IN VITRO NAM

- **ADME** — Individual mechanisms
- **MPS/3D** — Chip/Organoids
- **Ω** — Omics
- **PKDT** — Human PK/PD/ Tox Data

IN SILICO NAM

PBPK

- Predict pediatric PK/PD/DDIs
- Support dose selection

QSP / QST

- Predict efficacy/safety
- Inform trial design

QUANTITATIVE PROTEOMICS and METABOLOMICS — THE TRANSLATION HUB

Protein Abundance
DMET levels across tissues

Metabolomics
Biomarkers of enzyme/transporters

Genotype → Function
Links DNA to protein and metabolite

Scales the Models
Turns NAM data into human- parameters

HUMAN-RELEVANT PREDICTIONS

- Exposure / PK
- **Biomarkers**
- Efficacy
- Safety/Toxicity
- Pediatric PK/PD/DDI

Summary

- **Use of authenticated NAMs** is essential for successful IVIVE and reliable translation of data for improved drug development outcomes.
- **Quantitative proteomics:**
  - Enables precise, multiplexed measurement of ADMET-relevant proteins
  - Authenticates biological reagents by confirming identity and functional protein abundance, reducing risk of misleading in vitro findings.
  - Uncovers donor-dependent variability, aiding in lot selection and improving translational reliability.
  - Improves PBPK modeling and dose prediction, supporting precision medicine.
- **Measurement defines truth. Quantitation defines trust.**

Acknowledgements

CCHMC
- Darshak Gadara
- Dilip Singh
- Griffin Shaffer
- Sandhya Subash
- Takanori Takebe
- Masaki Kimura

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- Christy Watson
- Brian Karlberg
- Darren Melville
- Chandi Bandaranayaka

ALTIS Biosystems
BioIVT
Javelin Bio

PRINE Consortium: Proteomics-based Research Initiative for Non-Conserved Enzymes

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PRINCE 5.0 Potential Aims

1. Characterization of **complex in vitro models (NAMs)** for DMET abundance and activity
   - e.g., In-house organoids/MPS and NAM vendors
2. Role of non-conserved enzymes in the metabolism of **new drug modalities** (ADCs, PROTACs, Oligos, peptides, and other prodrugs)
3. Characterization of drug metabolism capacity of **human skin, endothelial cells, and muscle**: relevance to topical formulations, long-acting injectables, and low clearance drugs
4. Discovery and validation of **biomarkers** of non-conserved metabolizing enzymes

Project duration: Jan 1st 2027- December 31st, 2028